REMARKS

Summary of the Office Action

Claims 6-26 and 33-38 are pending in the application, of which claims 6-15 and 34-38 are under examination. Claims 16-26 and 33 are withdrawn from consideration as being drawn to a non-elected invention.

Claims 6-15 and 34-38 are rejected as lacking enablement under 35 U.S.C. § 112, first paragraph, and claims 6-8, 10, 11, 13-15, and 34-38 are rejected as lacking sufficient written description under 35 U.S.C. § 112, first paragraph. In addition, claims 6-10 and 34-38 are rejected as being indefinite under 35 U.S.C. § 112, second paragraph. In addition, claim 6 is objected to and the drawings are objected to for informalities.

Support for the Amendments

Claims 6 and 11 are amended herein and claims 7, 8, and 34-38 are canceled herein. Support for the amendments to claims 6 and 11 is found, e.g., at claim 7 as filed in the original specification, and, e.g., at page 6, lines 21-24, of the specification. No new matter has been added by these amendments.

Drawings

The Office Action states that Applicants are required to submit a proposed drawing correction in reply to the present Office Action, with respect to the Draftperson's Review of Patent Drawings, Form 948, attached to the Action mailed June 3, 2002; however, formal correction of the noted defects may be deferred until after the Examiner has considered the proposed drawing corrections.

In response, Applicants note that the Draftsperson's Review states that the Fig. 1 is objected to under 37 C.F.R. § 1.84(l) for poor line quality, and under 37 C.F.R. § 1.84(p) because the numbers and reference characters are not plain and legible. Other than improving the line quality and legibility of the numbers and reference characters, no actual corrections to the drawings are required by the Draftsperson. Submitted herewith for the Examiner's consideration

is an informal copy of a Replacement Sheet for Fig. 1A-1B. Applicants will file a formal version of this Replacement Sheet, if necessary, once the present application is allowed.

Objection to Claim 6

Claim 6 is objected to for informalities, specifically, because the recited Markush group requires formatting corrections. As amended herein, claim 6 no longer recites a Markush group. Accordingly, the objection is now moot and Applicants respectfully request its withdrawal.

Rejections Under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 6-15 and new claims 34-38 are rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. The rejection is based upon the reasons of record, as set forth in the previous Office Action, issued June 3, 2002. In essence, the rejection hinges on the assertion that the claimed methods encompass a method of importing any biological molecule, including a nucleic acid, into a cell in a subject. Delivery of a nucleic acid into a cell *in vivo* for therapeutic purposes is considered to be gene therapy; therefore, the claims are deemed to encompass gene therapy, which, the Office Action asserts, is an unpredictable art (see June 3, 2002 Office Action, last paragraph of page 4, through page 6; see also present (February 24, 2003) Office Action, pages 4-5).

While Applicants firmly believe that the claims as previously pending are enabled, in order to speed allowance of this application, Applicants have amended independent claims 6 and 11 to replace the phrase "importing a biologically active molecule" with the phrase "importing a peptide, polypeptide, or protein." Accordingly, the claims no longer encompass nucleic acid delivery and gene therapy methods, and this basis for the rejection is now moot. The claims as amended herein are fully enabled for delivery of a peptide, polypeptide, or protein into the cell of a subject; therefore Applicants request that the rejection be withdrawn.

The Office Action asserts that targeting the complex to the desired cells to achieve a therapeutic effect and avoiding systemic importation into all cells is critical, and that neither the prior art nor the instant specification provide sufficient guidance in this regard. In response, Applicants respectfully point out that avoiding systemic importation into all cells is *not* critical to the invention, nor does the specification state that such avoidance is critical to the invention. In

fact, the specification merely states that "any selected cell into which import of a biologically active molecule would be useful can be targeted by this method, as long as there is a means to bring the complex in contact with the selected cell. Cells can be within a tissue or organ, for example, supplied by a blood vessel into which the complex is administered" (see Specification, page 14, lines 13-17). The specification goes on to state that the cells of the lung epithelium can be targeted by inhalation of the complexes, or the complexes can be administered directly to a target site in the body. The specification also states that signal peptides that are known to be utilized by the selected target cell can be used (see page 14, lines 17-28); however, nowhere does the specification state that such target-specific signal peptides *must* be used, and nowhere does the specification state that the complexes cannot be systemically delivered, or that certain types of cells must be avoided. Accordingly, the statement that "avoiding systemic importation into all cells is critical" is not accurate. By "targeting selected cells" the specification merely means that the necessary cells must be exposed to and able to take up the delivered peptide. Moreover, as stated in the specification (see, e.g., page 8, line 2, through page 10, line 18), for *in vivo* administration, the peptides can be delivered by routine methods, e.g., parenterally, intravenously, by inhalation, by subcutaneous or intramuscular injection, by topical administration, by oral administration, etc.

As evidence that such systemic administration can be used to effectively deliver biologically active molecules to cells in a subject, Applicants refer to the Declaration of Jack Jacek Hawiger, M.D., Ph.D., submitted herewith. In his Declaration, Dr. Hawiger, an inventor of the present application, describes an *in vivo* experiment in which a peptide containing an importation competent signal sequence, coupled to a nuclear localization signal from NF-κB, was systemically administered to mice suffering from septic shock. Mice treated with this functional peptide, denoted SN50, showed an increased rate of survival, as well as protection from the fulminant liver injury that is a hallmark of this model of septic shock, systemic inflammation and tissue damage. Accordingly, biologically active molecules, such as peptides and polypeptides, are efficacious when administered to *in vivo* cells via systemic delivery to a subject.

The Office Action also states that, because Applicants only speculate that all signal peptides will function as importation competent signal peptides, having demonstrated it only for

Kaposi fibroblast growth factor, a skilled artisan will have to determine if any other known signal peptide can function as an importation signal, and that it would provide a large quantity of trial and error experimentation to do so.

In response, Applicants point out that, given the teachings of the specification, together with what was already known in the art, only *routine, permissible experimentation* would have been required to identify additional importation competent signal peptides. As described by the specification, an "importation competent signal peptide" is generally of a length of about 10 to about 50 amino acid residues and contains a hydrophobic, lipid-soluble portion (typically about 55-60% hydrophobic residues). As is well known in the art, a signal peptide is capable of penetrating through the cell membrane to allow the export of cellular proteins. The importation competent signal peptides of the invention are capable of penetrating through the cell membrane from the outside of the cell to the interior of the cell (see the specification, e.g., at page 10, line 20, through page 11, line 13). Signal peptides can be selected by methods that were well known in the art at the time the present application was filed, e.g., from the SIGPEP database (see page 11, lines 15-16 of the specification). Moreover, any selected signal peptide can be tested for its ability to function as an importation competent signal peptide, using routine screening methods that employ the *in vitro*, *ex vitro*, and *in vivo* teachings set forth throughout the entire specification, including the Examples, together with what was already known in the art. Accordingly, identification of additional importation competent signal peptides is *routine experimentation*, not undue experimentation, and the present methods, as claimed herein, are fully enabled in this regard.

Applicants note that claims 7, 8, and 34-38 are canceled herein; therefore, the rejection is now moot with regard to these claims. In view of the amendments and discussion set forth above, Applicants believe that pending claims 6 and 9-15 are enabled, and respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejections Under 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 6-8, 10, 11, 13-15, and new claims 34-38 are rejected under 35 U.S.C. § 112, first paragraph, as lacking sufficient written description. The rejection contains several bases, each of which will be individually addressed below.

a) Claims 6-8, 10, 11, and 13-15 are rejected under 35 U.S.C. § 112, first paragraph, as lacking sufficient written description. The Office Action asserts that the specification does not teach a structure-function correlation between specific amino acids and the importation function of the signal peptide, and, therefore, concludes that Applicants did not have possession of the entire genus of importation competent signal peptides, but only a method for how to identify an importation competent signal peptide experimentally.

In response, Applicants assert that: (1) the specification indeed provides an adequate written description of the importation competent signal peptides to be used in the claimed method, (2) notwithstanding this, the specification need not provide a written description of the importation competent signal peptides to be used in the claimed method because it is only the *claimed method* itself that must be described, and (3) the specification need not provide a written description of the importation competent signal peptides to be used in the claimed method because the peptides are only involved in *making and using* the claimed method (which is the subject of the enablement requirement) and are not the claimed method itself (which is all that need be described to satisfy the written description requirement).

The Legal Standard

The application must contain a "written description" of the claimed invention. 35 U.S.C. § 112, first paragraph. The essential goal of this written description requirement is to clearly convey the information that an applicant has invented the subject matter which is claimed. *See In re* Barker, 559 F.2d 588, 592 n.4, 194 USPQ 470, 473 n.4 (CCPA 1977). Another objective is to put the public in possession of what the applicant claims as the invention. *See* The Regents of the University of California v. Eli Lilly and Co., 119 F.3d 1559, 1566; 43 USPQ2d 1398, 1404 (Fed. Cir. 1997) (hereafter, "*Lilly*"). *Lilly* established that, in the case of claims to genes, an adequate written description requires more than the name of the gene and a statement of its function. *Lilly*, 119 F.3d at 1168; 43 USPQ2d at 1406. The court in *Lilly* required some physical description of the gene (such as its nucleotide sequence). While *Lilly* has been viewed by some as establishing a strict rule that the structure of any claimed biological molecule must be provided in an application, such a reading is both incorrect and inconsistent with precedent.

The Patent Office undertook a review of the written description caselaw in view of *Lilly* in order to establish guidelines for the examination of patent applications for compliance with the written description requirement of 35 U.S.C. § 112, first paragraph. *See* Guidelines for Examination of Patent Applications Under 35 U.S.C. 112, ¶1 "Written Description" Requirement, 66 Fed. Reg. 1,099 (Jan. 5, 2001) (hereafter, "Written Description Guidelines"). Far from requiring any absolute or *per se* requirement for adequate written description, the resulting Written Description Guidelines provide a case-specific and fact-dependent inquiry. This is consistent with caselaw, where compliance with the written description requirement is consistently referred to as a fact-dependent inquiry. *See, e.g.*, Vas-Cath v. Mahurkar, 935 F.2d 1555 (Fed. Cir. 1991). Thus, and in particular, the Written Description Guidelines are concerned with not requiring broad or strict structural description in many cases.

The standards embodied in the Written Description Guidelines in general, and in Example 16 of the Synopsis of Guidelines in particular, have recently been adopted by the Federal Circuit as valid for the analysis of compliance with the written description requirement. *See* Enzo Biochem v. Gen-Probe, 296 F.3d 1316, 1324 (Fed. Cir. 2002) (hereafter, "*Enzo II*"). On this point the court in *Enzo II* states that "it is not correct...that all functional descriptions...fail to meet the written description requirement." *Id.* at 1324. Thus, a claim to method that includes the step of administering to the subject a complex comprising a peptide, polypeptide, or protein linked to a mammalian hydrophobic importation competent signal peptide as functionally and structurally defined by the specification (e.g., at page 10, line 20, through page 21, line 16), is adequately described even in the absence of description of the structure-function correlation between specific amino acids and the importation function of the signal peptide, as required by the Office Action.

A Claim to a Method Does Not Require Description of the Structure of Compounds Used in the Method

The first paragraph of 35 U.S.C. § 112 requires "a written description of the *invention*." The invention is what is claimed. Claims can be drawn to various types of inventions, including, for example, claims to compositions *per se* and claims to methods. A composition is a physical object, which has a physical structure. A method is a process made up of one or more process steps (that is, one or more acts to be carried out). Thus, the written description of a composition

invention typically requires at least some description of the structure of the composition (because a composition (e.g., a structure) is what the invention is), and the written description of a method invention requires description only of the acts to be performed (because a method (e.g., one or more acts) is what the invention is). This distinction is supported by the Written Description Guidelines, in which the first step in the analysis of compliance with the written description requirement is to "[d]etermine whether the application as filed describes the complete structure (*or acts of a process*) of the claimed invention as a whole." Written Description Guidelines at 1106 (emphasis added). Nothing in the statute or the caselaw requires a written description of anything other than the *claimed invention* for compliance with the written description requirement. Thus, only the process steps of a claimed method need be described in order to satisfy the written description requirement for a method.

The Requirement That the Manner and Process of Making and Using the Claimed Invention Be Described Is Not Part of the Written Description Requirement

The courts have clearly established that the first paragraph of 35 U.S.C. § 112 includes, *inter alia*, two separate requirements: (1) an enablement requirement based on the statutory language that the application describe "the manner and process of making and using [the invention], in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same," and (2) a written description requirement based on the statutory language "[t]he specification shall contain a written description of the invention" (the third requirement of the first paragraph of 35 U.S.C. § 112, the "best mode" requirement, is not relevant here). The separate status of the make and use clause and the written description clause was at the heart of the recognition of the separate written description requirement. *See* Vas-Cath v. Mahurkar, 935 F.2d 1555, 1560-61 (Fed. Cir. 1991); Enzo Biochem v. Gen-Probe, 285 F.3d 1013, 1018, 1021 (Fed. Cir. 2002) (hereafter "*Enzo I*"). Specifically, the court in *Vas-Cath* begins its discussion of the separateness of the written description requirement by quoting the entire first paragraph of 35 U.S.C. §112 but emphasizing the phrase "a written description of the invention." *Id.*, at 1560. The court then notes that "[a]pplication of the 'written description' requirement, *derived from the portion of § 112 emphasized above*, is central to resolution of this appeal." *Id.* (emphasis added).

The separate status of the written description requirement and the enablement requirement (as embodied by the different clauses of 35 U.S.C. § 112, first paragraph, discussed above) was also discussed in *In re* Barker, 559 F.2d 588, 594 (CCPA 1977) (Rich, J., concurring). Judge Rich noted that long before section 112 was written, and before claims became the standard means of setting forth the metes and bounds of inventions, the original patent laws included language almost identical to the written description clause and enablement clause of 35 U.S.C. § 112, first paragraph. *See id.* Before the use of claims became common, it was the description of the invention in the specification in general that defined what the applicant considered to be his invention. *See id.* Thus, the written description clause in the early patent laws required a definition of the invention in the specification to serve the same purpose as claims do under current law. The written description clause was retained when section 112 was written despite the fact that claims had long since taken on the function of defining the invention. *See id.* For this reason, Judge Rich argued in *Barker* that, until the revival of the written description requirement in its current form, the first clause of 35 U.S.C. § 112, first paragraph, was "superfluous words" that had been retained in section 112 when it was written because "they were familiar and had many times been construed." *Id.* By this, and relevant here, Judge Rich meant in part that the words were superfluous to the enablement requirement, which had remained a consistent requirement in patent applications from the earliest patent laws. Thus, a description of the manner and process of making and using a claimed invention is an aspect of the enablement requirement but not of the written description requirement.

The Claimed Methods are Adequately Described by Description of the Method Step

As discussed above, the first paragraph of 35 U.S.C. § 112 requires "a written description of the *invention*." The invention here is a method including a single step, i.e., administering to the subject a complex comprising a peptide, polypeptide, or protein linked to a mammalian hydrophobic importation competent signal peptide. Thus, written description of the claimed method requires description only of the act to be performed because the act to be performed in the claimed method is what the invention is. Nothing in the statute or the caselaw requires a written description of anything other than the *claimed invention* for compliance with the written description requirement. As an aside, and as discussed in detail hereinabove, Applicants note

that whether those of skill in the art can succeed in carrying out the acts of the method and achieve the claimed results is solely a question of enablement.

As discussed above, the specification provides a description of the method step. Applicants submit that the step of administering to a subject a peptide, polypeptide, or protein linked to an importation competent signal peptide is adequately described in the specification (e.g., at page 8, line 2, through page 10, line 18). For at least these reasons, Applicants asserts that the claimed method is adequately described.

Identification of Additional Importation Competent Signal Peptides Does Not Implicate the Written Description Requirement

As stated above, the claimed methods only require administration to a subject of a peptide, polypeptide, or protein linked to a mammalian hydrophobic importation competent signal peptide, and, Applicants submit, only requires written description of the method step (that is, administration). Applicants assert that the other aspect of the claimed method (i.e., importation competent signal peptides to be used in the claimed method) implicates only the enablement requirement of 35 U.S.C. § 112, first paragraph, because they involve not the claimed method itself, but rather how to make and use the claimed method.

As discussed above, the written description requirement and enablement requirement are distinct requirements based on different clauses of 35 U.S.C. § 112, first paragraph. In particular, the requirement of a description of the manner of making and using the claimed method is not a part of the written description requirement. Thus, features of the claimed method that involve how to make and use the method need not be described according to the requirements of written description. The claim requires that the peptide, polypeptide, or protein be imported into the cell of the subject. This is an *effect* of the method, not a step of the method. Obtaining this effect is solely an issue of enablement, not written description. The effect is not a step or act required to perform the method, it is only a result that those of skill in the art must be able to *obtain* (without the need for undue experimentation) *when* they practice the claimed method (that is, *when they perform the step* of the method). Those of skill in the art must practice the method so as to obtain the claimed effect. This is a feature of the *use* of the claimed method, not of the method step *per se*, and as such, is only a feature of how to use the claimed method. Because how to use the claimed method is not a part of the written description

requirement, such use is not a proper area of inquiry in assessing written description of the claimed method.

For similar reasons, the *implied* functional characteristics of the importation competent signal peptides of the invention (that is, the ability to transport a peptide, polypeptide, or protein in the cell of a subject) that will achieve the effect of the claimed method is only an issue of enablement because it is only an issue of "the manner and process of making" the claimed method. That is, how to make the importation competent signal peptides is at most only an aspect of how to "make" the claimed method because the materials to be used in a method are arguably part of "making" such a method. Making the materials used in a claimed method is clearly not the method itself or a step in the method. In this regard, Applicants note the distinction between a method such as the claimed method (where there is no step of making or producing the importation competent signal peptides) and a method where production of a material used in the method is an explicit step of the method. Because how to make the claimed method is not a part of the written description requirement, such use is not a proper area of inquiry in assessing written description of the claimed method. For at least these reasons, Applicants assert that the invention as claimed herein is adequately described. Moreover, as discussed above with regard to the enablement rejection, the claimed method is *enabled* with regard to its recitation of an importation competent signal peptide, because, given the teachings of the specification, together with what was already known in the art, only *routine, permissible experimentation* would have been required to identify additional importation competent signal peptides.

In view of the above, the specification provides sufficient description of pending claims 6, 10, 11, and 13-15 (claims 7, 8, and 34-38 are canceled herein), and this basis of the written description rejection can be withdrawn.

b) Claims 6-10 and 34-38 are rejected under 35 U.S.C. § 112, first paragraph, as lacking sufficient written description, because claim 6, as amended in the previous Reply, recited "a vaccine polypeptide," wherein the complex induces or inhibits a biological response including "a mitogenic response in the cell," "an inhibition of cell division in the cell," and "an inhibition of tyrosine phosphorylation in the cell," all of which the Office Action has deemed new matter.

Claim 6, as amended herein, does not recite the above-listed phrases and does not contain new matter. Claims 7-8 and 34-38 are canceled herein, and the remaining rejected claims, i.e., claims 9-10, depend from claim 6. Therefore, this aspect of the rejection can now be withdrawn.

c) Claims 6-10 and 34-38 are rejected under 35 U.S.C. § 112, first paragraph, as lacking sufficient written description, because claim 6, as amended in the previous Reply, is drawn to a method of importing a biologically active molecule into a cell, wherein the biologically active molecule is selected from the group that includes "an antigenic polypeptide" and "a portion of a protein." The Office Action asserts that the disclosure is not deemed to be descriptive of the complete structure of a representative number of species encompassed by the claims, because the skilled artisan cannot envision all antigenic polypeptides and portions of a protein based on the teachings of the specification.

While Applicants do not agree that one of skill in the art would not be able to envision the claimed antigenic polypeptides and protein portions based on the specification, together with what was known in the art, independent claim 6, as amended herein, no longer recites the phrases "an antigenic polypeptide" and "a portion of a protein." As stated above, Claims 7-8 and 34-38 are canceled herein, and the remaining rejected claims, i.e., claims 9-10, depend from claim 6. Accordingly, the rejection is now moot, and can be withdrawn.

In view of the above, Applicants believe that pending claims 6, 9-11, and 13-15 are allowable under 35 U.S.C. § 112, first paragraph, and respectfully request that the written description rejection be withdrawn.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 6-10 and 34-38 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. Specifically, independent claim 6 is deemed vague and indefinite on two bases: first, in that claim 6 does not employ proper Markush language, and second, in its recitation of a "vaccine polypeptide."

Claims 34-38 are canceled herein. Claim 6, as amended herein, no longer recites a Markush group, and no longer recites a "vaccine polypeptide." Accordingly, the rejection is now moot and can be withdrawn.

CONCLUSION

In view of the above amendments and remarks, reconsideration and allowance of the pending claims is believed to be warranted, and such action is respectfully requested. The Examiner is encouraged to directly contact the undersigned if this might facilitate the prosecution of this application to issuance.

A Request for a Three Month Extension of Time to extend the period for response by three months to August 25, 2003 (since August 24, 2003 fell on a Sunday) is enclosed. A Notice of Appeal and Credit Card Form PTO-2038 authorizing payment in the amount of $625.00 ($465.00 for the three-month extension of time fee and $160.00 for the Notice of Appeal fee) are also enclosed. No additional fees are believed due. However, the Commissioner is hereby authorized to charge any deficiency or to credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence, including any items indicated as being attached or enclosed, is being transmitted via First Class U.S. Mail to: Mail Stop AF, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Shari J. Corin, Ph.D. — Date: August 25, 2003